Bringing Personalized Oncology to Cancer Prediction — and Prevention

Cancer geneticists, epidemiologists and oncologists team up to use mutation rate to predict individual cancer risk.

October 23, 2018 By Sabrina Richards

We all know that smoking increases lung cancer risk. And certain BRCA variants increase breast cancer risk. But not every smoker, or every person carrying a worrisome BRCA genetic variant, will get cancer. What links these two risk factors are DNA damage and errors made when DNA is replicated. Both leave permanent changes, or mutations, on our genetic blueprint. A clearer picture of an individual's mutations could give a clearer idea of that person's cancer risk.

Scientists at Fred Hutchinson Cancer Research Center are teaming up to see if they can help paint that picture for patients. Jason Bielas, PhD, recruited colleagues in and outside the Hutch in brain cancer, epidemiology and biostatistics to garner a $2.4 million grant from the National Institute of Environmental Health Science and the National Cancer Institute to employ his error-free DNA-sequencing technology to measure patients' personal mutation rate and link this to individual cancer risk.

"The idea is to apply some of this advanced technology to population science," said Bielas, a cancer geneticist in the Public Health Sciences and Human Biology divisions at Fred Hutch. The idea is, "if we can monitor how people's genomes evolve, or their innate mutation rate, we could probably predict their risk of developing cancer."

Discovering the genome's mutagenic dosimeter

What Bielas ultimately envisions is a quick and easy blood test that gives each person a window into how quickly their DNA is mutating. This would allow doctors to more closely monitor an individual for cancer, or perhaps help that patient make a risk-reducing change to their environment, such as giving up smoking.

But that's still years away. To begin with, Bielas and his collaborators, Christopher Li, MD, PhD, Garnet Anderson, PhD, and Wei Sun, PhD, in the Public Health Sciences Division, Eric Holland, MD, PhD, in the Human Biology Division, and Michael Weller, MD, at University Hospital Zurich, must first better understand mutation in humans — where it occurs, how frequently it occurs, and how exposure to mutagens like cigarette smoke influences this.

The team will be “essentially looking at mutagenesis throughout the genome, and how the genome evolves,” Bielas said. Doing this in humans is “a huge step forward.”

A first step will be narrowing their focus from the genome’s entire DNA sequence to the key areas that reflect the total mutation rate.

These areas will act as “dosimeters,” providing a recording of how much an individual is being exposed to DNA-damaging and mutating agents such as cigarette smoke, he said. “They’ll be able to predict how the entire genome is mutating.”

Proving the principle in people

The next open question is whether blood cells, the basis of the simple test Bielas envisions, are a good proxy for cancer risk elsewhere in the body. The team has developed two proof-of-principle studies to begin testing the approach. One will concentrate on the influence of smoking-related mutation rates on lung cancer development, drawing on samples from the Women’s Health Initiative, or WHI. The other will examine the influence of chemotherapy-caused mutations on development of secondary cancers in brain cancer patients undergoing treatment.

Li is working with Bielas to correlate smoking exposure, measured in pack-years (the number of cigarettes smoked per day divided by the years of smoking), with lung cancer development in participants of the WHI study. If it turns out that smoking causes changes in the mutation rate of blood cells that reflect what’s happening in the lung, the results could be quickly translated into better health outcomes, he said.

A test that reveals which smokers have high mutation rates, and therefore are at higher risk for developing lung cancer, could help doctors figure out which patients would most benefit from screening strategies designed to detect cancer early, Li said.

“In an ideal world, this approach would improve individual-level risk assessment. It would combine an exposure that we know is related to cancer risk with this molecular assessment,” he said.

Chemotherapy is another environmental exposure that is known to damage DNA and, ironically, lead to cancer. The second pilot study will be done in brain cancer patients who are receiving standard chemotherapy to treat their disease. Chemotherapy’s negative side effects, such as the suppression of blood- and immune-forming cells in the bone marrow, may correlate with mutation rates in blood cells.

If so, a personalized mutation rate could help oncologists personalize chemotherapy as well. Perhaps one patient’s healthy cells resist chemo’s DNA-damaging effects and could withstand a higher, more effective dose without raising their risk of secondary cancer. Oncologists armed with early knowledge about chemo’s effects on DNA could quickly switch patients who are deemed sensitive to one regimen to another drug that causes less damage, Bielas hypothesizes.

A wide horizon

If the work pans out, it could have wide-ranging benefit, said the researchers.

The approach “could be readily applicable to other sorts of exposure–disease relationships,” such as alcohol and cancer, Li said.

Additionally, the types of mutations that occur could reveal specific environmental exposure or innate defects in DNA repair, Bielas said. Certain mutagens or repair defects leave characteristic types of mutations behind, allowing researchers to infer what caused the damage in the first place.

“That’s what’s been missing, the link between exposure, mutations, and cancer,” he said. “That’s what we’re trying to bring together.”

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